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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,547	01/23/2002	Arthur L. Castle	GLC0002-US	1223

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,547	CASTLE ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6-10 and 23-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6-10 and 23-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08 June 2006 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 2-4, 6-10, and 23-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of analysis of the effect of compounds on gene expression in which a change in gene expression progresses in a same direction with time and increased dose and does not change direction at adjacent time points. On page 29, lines 17-20 the specification recites:

> To be useful, a pattern must demonstrate time stability. In that regard, the change in gene expression should go in the same direction for two or more time points and not change direction in adjacent time points relative to the time points where gene expression is changing.

The amendment to the claims filed 08 June 2006 adds the limitation that the gene expression change "does not change direction at adjacent time points." This new limitation is broader than that recited in the specification passage quoted above. For example, it may be that the adjacent time points could be at any two adjacent time adjacent time points in a data set, which does not allow for a change in direction at any point in the measured time span.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2-4, 6-10, and 23-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-4, 6-10, and 23-37 are drawn to a method of analysis of the effect of compounds on gene expression in which a change in gene expression progresses in a same direction with time and increased dose and does not change direction at adjacent time points. The metes and bounds of the claimed subject matter are not clear because it is not clear what the adjacent time points are adjacent to, and are further unclear regarding what is a change in direction. A change in direction could be a change in a rate of increase or a change in a rate of decrease, or a change from an increase or decrease to a steady level from one time point to the next.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 2-4, 7-9, 24-28, 30, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al.

The claims are drawn to a method of assessing toxicity of a compound comprising determining the effect of varying both time and dose of a compound on gene expression. The change in gene expression does not change direction at adjacent time points, which for the purpose of examination is interpreted to read on data with four successive increasing or decreasing time point values of gene expression. In some embodiments the number of genes is greater than 10, the gene expression data is time stable, contrast analysis, cluster analysis, and principal component analysis is employed, treated liver, kidney, brain, spleen, pancreas, and lung samples are used, the compound is acetaminophen, and factor analysis is used.

Cunningham et al. shows in columns 1-2 a method of comparing the effect of a known toxic compound and a putative toxic compound on gene expression of a treated cell. Microarray polynucleotide hybridization assays are used to assess gene expression. Preferred tissues are listed as liver, kidney, brain, spleen, pancreas, and lung. A preferred toxic compound is

acetaminophen. Cunningham et al. shows SEQ ID NOS: 1-61 on column 4 as targets to be assayed for toxic regulation. Cunningham et al. shows clustering of target genes in column 4. As contrast analysis is defined in the specification on page 8 as analysis of genes that are grouped by their response pattern to the toxic compound, Cunningham et al. shows cluster analysis in Tables 1-3 in columns 14-15. Cunningham shows data in Tables 2 and 3 (columns 14-15) in which genes are assayed which have four successive time points of increasing or decreasing values (see SEQ ID NOS: 3, 4, 40, 59, 6, and 55) Cunningham et al. shows in column 12 that rats were treated for different times with acetaminophen before sacrifice and mRNA isolation. Time variation is a factor analyzed by Cunningham. Cunningham et al. does not show use of principal component analysis or variation of dose and time.

Hilsenbeck et al. show in the abstract and throughout the use of principal component analysis to determine those genes that varied the most between two experiments. Hilsenbeck et al. treated mice with breast cancer cells, and then treated the mice with tamoxifen. The mice were sacrificed at various times and mRNA was isolated and analyzed by use of a polynucleotide microarray to assess changes in gene expression during the experiment (see pages 453-454). Hilsenbeck et al. used principal component analysis to determine which genes were the most varied when comparing different mRNA sample sets. Hilsenbeck et al. concludes on page 458 that "principal component analysis of log-transformed data provides a practical approach to data reduction, visualization, and identification of "significant" outlier genes."

Johnston et al. shows in the abstract and especially in figure 4 results of treatment of mice to ozone. A variety of genes were monitored for alterations in gene expression due to the ozone treatment, including eotazin, MIP-1alpha, and MIP-2. The dosage of ozone was varied and time

points at each level of ozone were taken. Figure 4 shows that in many instances expression of genes were both dose and time dependent. Johnston et al. concludes on page 95 that early responses to ozone exposure may be predictive of ozone toxicity due to the time and dosage dependence.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Cunningham et al. by use of principal component analysis to analyze the gene expression data because Hilsenbeck et al. shows that principal component analysis can be used to analyze gene expression data of toxicity experiments to determine those gene sets that are most varied by the treatment. It would have been further obvious to vary dose and time of treatment because Johnston et al. shows that when toxicity is determined to be time and dose dependent, initial responses may be predictive of later toxicity.

9. Claims 2 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above, and further in view of Holden et al.

The claims are drawn to analysis of the effect of carbon tetrachloride on gene expression.

Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above does not measure the effect of carbon tetrachloride on gene expression.

Holden et al. shows treatment of a hepatoma cell line with carbon tetrachloride, followed by isolation of mRNA and polynucleotide microarray analysis of the effect of carbon tetrachloride on gene expression in the treated cells. Forty genes were found to be affected.

Holden et al states that their method will allow for study of mechanisms of carbon tetrachloride toxicity.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above by use of carbon tetrachloride as the assayed compound because Holden et al. shows that carbon tetrachloride is a toxic compound that affects gene expression.

10. Claims 2, 10, 26, 28, 29, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above, and further in view of Machens et al.

The claims are drawn to analysis toxic compounds on gene expression that uses logistic regression.

Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above does not show use of logistic regression.

Machens et al. shows that use of logistic regression helps in detection of correlation between a patient's HLA genotype and thymic pathology in myasthenia gravis patients. Details of the statistical analysis are given on page 297.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of correlation of a toxic response to a compound and gene expression of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above by use of the logistic regression method of Machens et al. because Machens et al. shows that their method can be used to correlate genetic

data and disease state and for the purposes of the statistical analysis the data of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above is equally applicable to analysis by the method of Machens et al.

11. Claims 2, 23, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above, and further in view of Wikstrom et al.

The claims are drawn to analysis toxic compounds on gene expression that uses least squares analysis.

Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above does not show use of least squares analysis.

Wikstrom et al. shows that use of least squares analysis helps in detection of correlation of prognostic factors and ultimate development of prostate cancer. The use of least squares analysis is detailed on page 253.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of correlation of a toxic response to a compound and gene expression of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above by use of the least squares analysis method of Wikstrom et al. because Wikstrom et al. shows that their method can be used to correlate prognostic factors and disease state and for the purposes of the statistical analysis the data of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above is equally applicable to analysis by the method of Wikstrom et al.

12. Claims 2, 6, 26, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above, and further in view of Strehlow in view of Lockhart et al.

The claims are drawn to analysis of hybridization signals in which background correction is performed by averaging the background of a region of an array and further by use of mismatch controls.

Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above does not show analysis of hybridization signals in which background correction is performed by averaging the background of a region of an array and further by use of mismatch controls.

Strehlow shows software for analysis of microarray data. Strehlow shows background correction that uses either a global average or a local average on page 120.

Lockhart et al. shows use of mismatch hybridization controls to correct for nonspecific hybridization on page 1676.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of correlation of a toxic response to a compound and gene expression of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above by use of the local average method of background correction of Strehlow because Strehlow shows that background correction is useful to determine total differences between hybridization samples in an array. It would have been further obvious to use mismatch controls to correct for nonspecific hybridization because

Lockhart et al. shows such mismatch controls for each RNA analyzed in their method to correct for nonspecific signal intensity.

Response to Arguments

13. Applicant's arguments filed 08 June 2006 have been fully considered but they are not persuasive. The applicants state that Cunningham et al. does not show time points that do not change direction at adjacent time points, however Cunningham et al. shows such time points in Tables 2 and 3. It is further noted that the applicants point to instant figure 1 as an example of adjacent time points that do not change direction, but the figure appears to show no adjacent time points that are either increasing or decreasing in value. The applicant states that the combination of references does not show composite variables, however Hilsenbeck shows analysis of expression data of a plurality of genes by principal component analysis to derive composite vectors, and Cunningham et al. suggests a plurality of genes to monitor for toxic effects of compounds.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

John Brusca 9 July 2006

John S. Brusca
Primary Examiner
Art Unit 1631

jsb